

Demystifying Medicine 2009

HIV: The Epidemic Persists Globally and Locally

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and
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National Institutes of Health

January 27, 2009



CENTERS FOR DISEASE CONTROL
MNWR
MORBIDITY AND MORTALITY WEEKLY REPORT

June 5, 1981

Pneumocystis Pneumonia – Los Angeles

In the period October 1980 – May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and cardiac mucosal infection. Case reports of these patients follow.

July 4, 1981

Kaposi's Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City (NYC), 6 in California). The 26 patients range in age from 26–51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California) – all 8 within 16 months after KS was diagnosed.

The Washington Post

August 30, 1981

2 Mysterious Diseases Killing Homosexuals

By Philip J. Hilts

Two rare diseases have suddenly struck more than 100 homosexual men in the United States and killed nearly half of them, in a medical mystery that appears to be on the scale of the toxic shock syndrome or Legionnaire's disease.

1 June 1982

Volume 96

Number 6

Annals of Internal Medicine

Published Twice Monthly by the American College of Physicians

The Syndrome of Kaposi's Sarcoma and Opportunistic Infections: An Epidemiologically Restricted Disorder of Immunoregulation

Anthony S. Fauci, M.D.

"...because we do not know the cause of this syndrome, any assumption that the syndrome will remain restricted to a particular segment of our society is truly an assumption without scientific basis."

CENTERS FOR DISEASE CONTROL
MNWR
MORBIDITY AND MORTALITY WEEKLY REPORT

July 09, 1982

Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States

July 16, 1982

Pneumocystis carinii Pneumonia among Persons with Hemophilia A

December 10, 1982

Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) – California

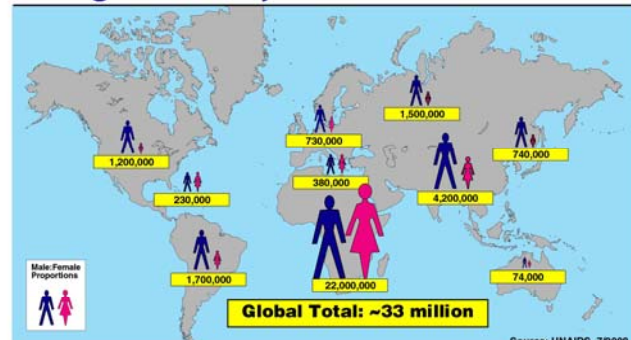
December 17, 1982

Unexplained Immunodeficiency and Opportunistic Infections in Infants – New York, New Jersey, California

January 07, 1983

Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS) – New York

Adults and Children Estimated to be Living with HIV, 2007

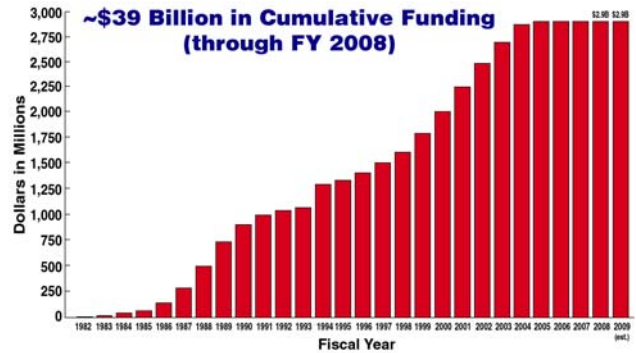


HIV/AIDS in the United States

- 545,805 cumulative deaths
- ~1.1 million living with HIV
 - 21% unaware of their infection
- ~56,300 new infections in 2006
 - 53% male-to-male sexual contact, 31% heterosexual contact
 - 45% blacks, 35% whites, 17% Hispanics
 - incidence rate among blacks 7 times higher than whites

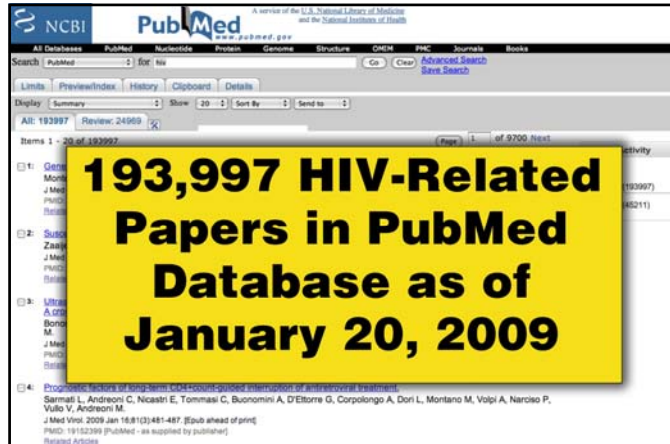
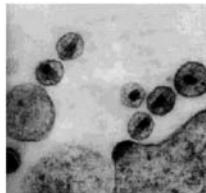
Source: CDC, Includes 50 states and District of Columbia

NIH HIV/AIDS Research Funding



Advances in AIDS Research, 1981-2009

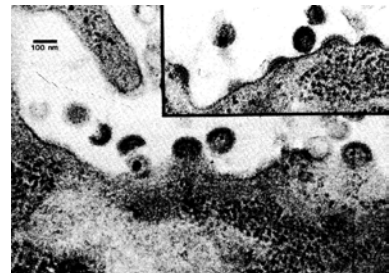
- Etiology
- Diagnosis
- Molecular Virology and Epidemiology
- Pathogenesis
- Natural History
- Treatment
- Prevention
- Vaccine Development



Discovery of HIV as the Cause of AIDS, 1983-84



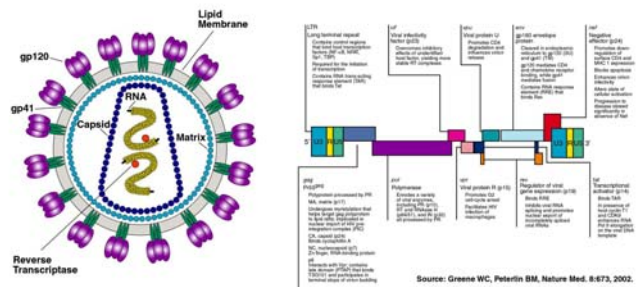
Electron Micrograph of Retrovirus Isolated from Lymph Node and Grown in Cord Blood Lymphocytes



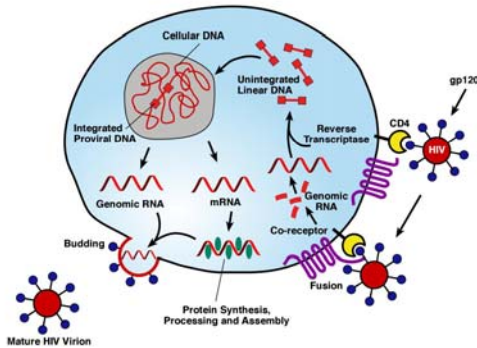
Source: Barre-Sinoussi et al. *Science* 220:868, May 20, 1983

Pathogenesis of HIV Infection

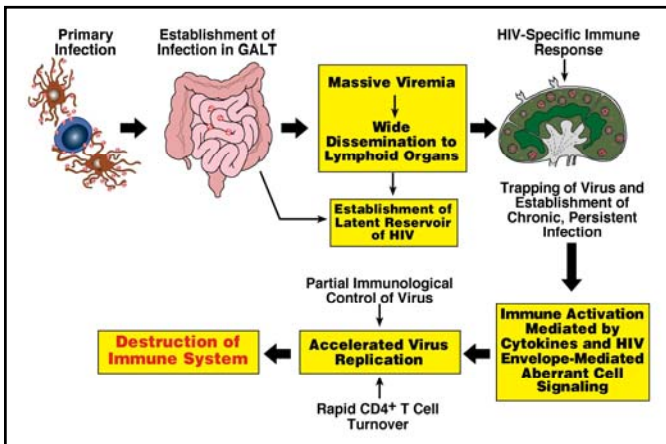
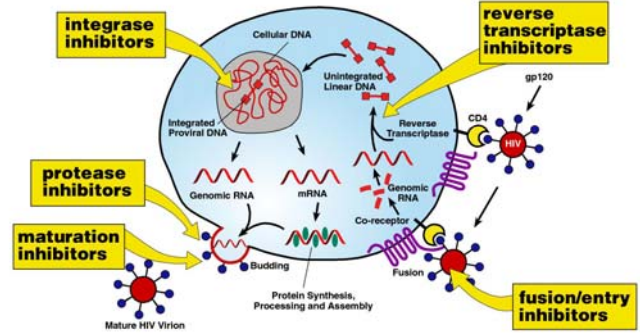
Organization of the HIV-1 Virion



The Replication Cycle of HIV



HIV Replication Cycle: Targets for Antiretroviral Therapy



PNAS
 Proceedings of the National Academy of Sciences
 of the United States of America
 September 28, 1999 | vol. 96 | no. 20 | pp. 10945-11638 | www.pnas.org

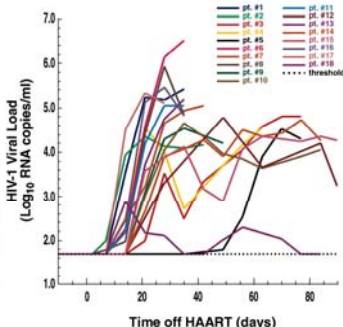
Perspective
Latent Reservoirs of HIV: Obstacles to the Eradication of Virus
 Tae-Wook Chun and Anthony S. Fauci

Rebound of HIV Following Discontinuation of Therapy

PNAS
Proceedings of the National Academy of Sciences
of the United States of America

HIV-1 and T Cell Dynamics after Interruption of Highly Active Antiretroviral Therapy (HAART) in Patients with a History of Sustained Viral Suppression

Richard T. Davey Jr., et al.



AIDS Drugs Have Saved 3 Million Years of Life in the United States

July 1, 2006
Volume 194

The Journal of
Infectious
Diseases

The Survival Benefits of AIDS Treatment in the United States

RP Walensky et al.

Patient: Introduction and Interview

Index Case 27 Year-Old Hospital Security Guard

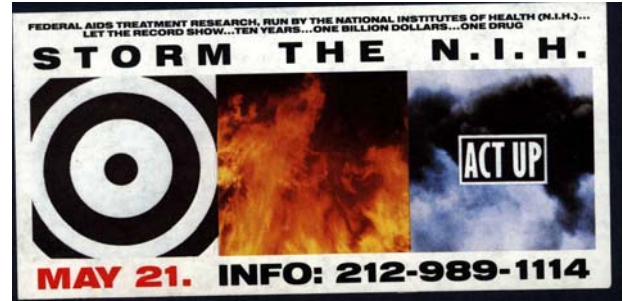
Date: April 1979
CC: Fever and shortness of breath x 2 months
PI: Excellent health
White plaques in mouth for weeks
PMH: Amebiasis x 1 (no travel)
PX: Fever, diffuse rales
Lab: Diffuse infiltrates/hypoxemia
Dx: Attending
1. Fungus
2. TB
3. Non infectious inflammatory pneum

Patients Die from Frequent, Severe Opportunistic Infections

- Opportunistic Infections
 - Unusual frequency
 - Unusual severity
- AIDS = Unique Cluster of OIs
 - Oral Candidiasis
 - Pneumocystis pneumonia
 - Mycobacterium avium complex
 - CMV Retinitis
 - Toxoplasma Encephalitis

New Pathogens Emerge

- Cryptosporidia
- Microsporidia
- JC virus
- HHV-8
- HHV-6
- Bartonella



Potential Drugs for HIV Emerge: Suramin, HPA-23, Ampligen, Cyclosporin

THE WALL STREET JOURNAL

French Firm Hopes Possible AIDS Drug Will Be Cleared for Tests in U. S. in Fall

A French drug company said it hopes to begin "limited clinical trials" this fall in the U. S. of the experimental drug HPA-23, which has drawn ailing film star Rock Hudson and other Americans to Paris for treatment of acquired immune deficiency syndrome.



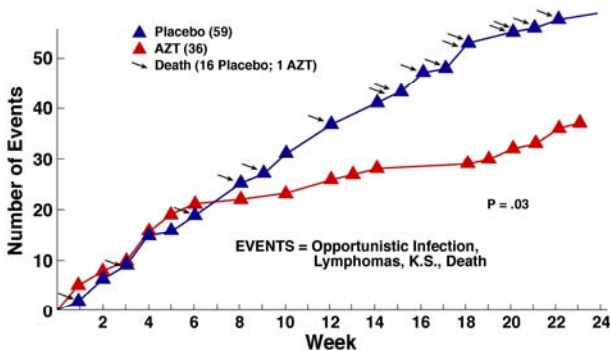
Medicine

Furor Over an Aids Announcement

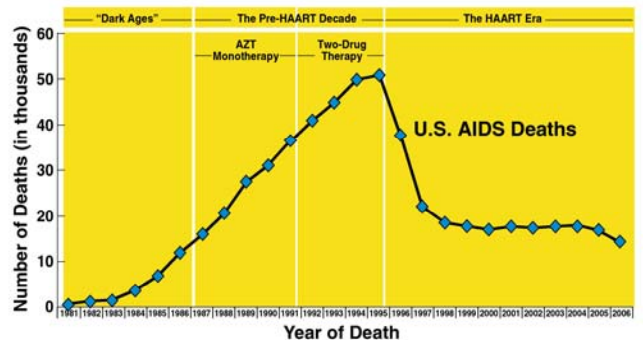
Critics say a claim by French doctors is premature
By CLAUDIA WALLIS

Nov. 11, 1985

Serious Events/All Patients



AIDS Therapy: the "Dark Ages", the Pre-HAART Decade, and the HAART Era



FDA-Approved Antiretroviral Drugs

NRTI

- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

NNRTI

- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine

PI

- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Fusion Inhibitor

- Enfuvirtide (T-20)

Entry Inhibitor

- Maraviroc

Integrase Inhibitor

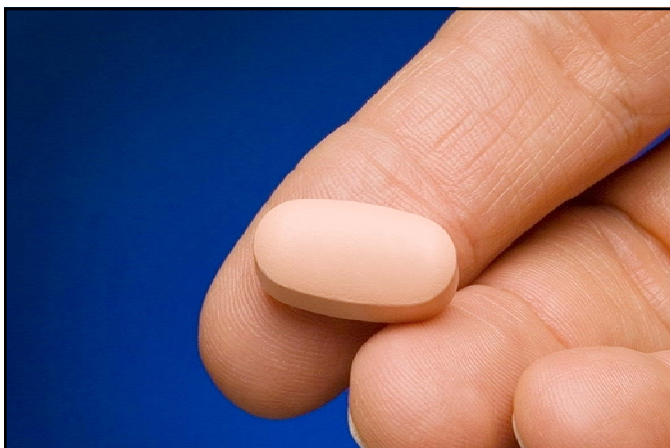
- Raltegravir

Combinations

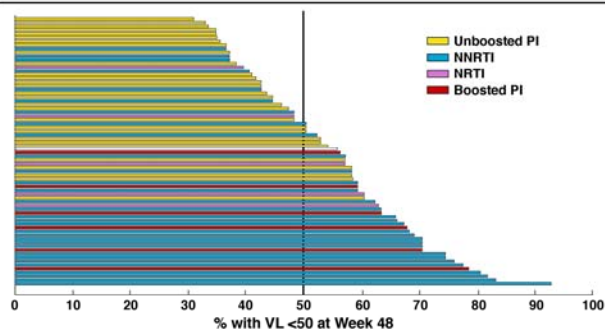
- 6 available, combining 2 or 3 drugs



How Many Antiretroviral Drugs for HIV Infection?

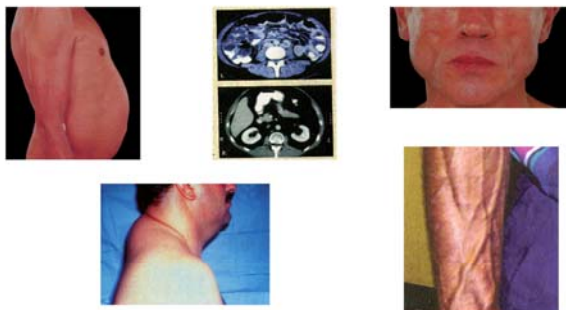


Percent of Patients with Plasma HIV-1 RNA ≤ 50 copies/mL at Week 48 in 49 Trials



Bartlett JA et al. 12th CROI 2005, Abstract 586.

Physical Manifestations of Fat Redistribution Syndromes



Antiretroviral Therapies State of the Art

- When to start?
- What to start?
- When to change?
- What to change to?

When to Start

Case for Earlier Initiation of Therapy

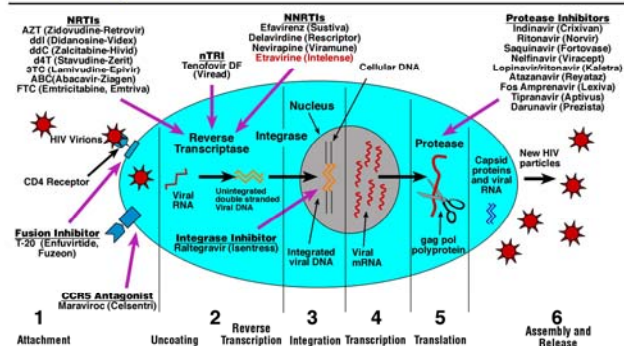
- Superior immune reconstitution
- Fewer complications of therapy at high CD4
- Association of ongoing viremia with inflammation and adverse effects
- Potential public health benefit

Case for Delaying Therapy

- Short-term and long-term toxicity
- Risk of
 - virologic failure
 - resistance
 - cross-resistance
- Uncertainty about long term benefit

What to Start

HIV Replication Cycle and Sites of Drug Activity



Antiretroviral Strategy

- What is best for individual patient
- What is best for community

Public Health Benefit of ART

- Reduce sexual transmission of HIV by reducing HIV viremia and shedding
- Reduce the fitness of HIV
- Reduce incidence of new cases

Holmberg SD et al. *Clin Infect Dis.* 2004;39:1699-1704.

Washington, D.C Our Nation's Capital



The Washington Post

November 26, 2007

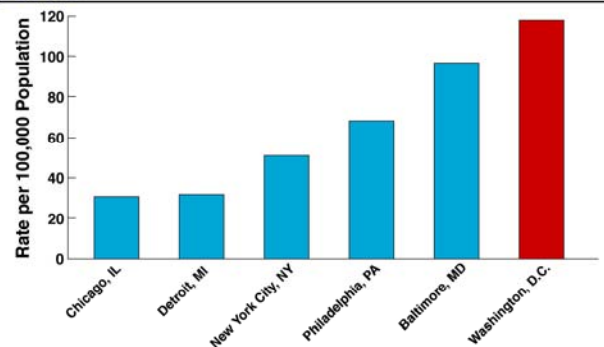
Study Calls HIV in D.C. a “Modern Epidemic”

The New York Times

November 27, 2007

Report Finds Washington Has Highest AIDS Infection Rate Among U.S. Cities

Rates for Newly Reported AIDS Cases 2005

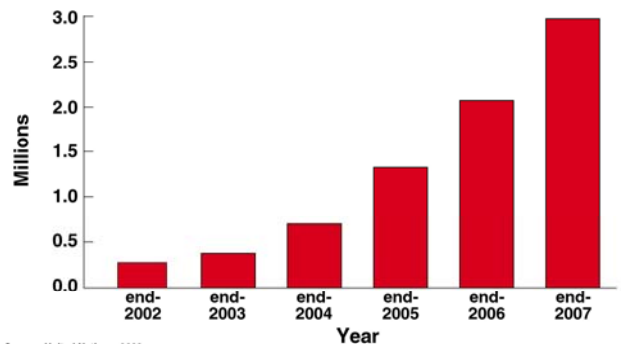


HIV Prevalence Rates in 15 PEPFAR Focus Countries, 2008 (Age 15-49 Years)

Country	Percent Infected
Botswana	23.9
South Africa	18.9
Namibia	15.3
Zambia	15.2
Mozambique	12.5
Tanzania	6.2
Uganda	5.4
Kenya	4.9
Cote D'Ivoire	3.9
Nigeria	3.1
Rwanda	2.8
Guyana	2.5
Haiti	2.2
Viet Nam	0.5

← DC AA = 5.0%

Number of People Receiving Antiretrovirals in Low- and Middle-Income Countries, 2002-2007



Source: United Nations, 2008

Despite major advances in access to anti-HIV drugs in low- and middle-income countries, only ~30% of people in these countries who need such drugs according to accepted medical criteria are receiving them.



Prevention

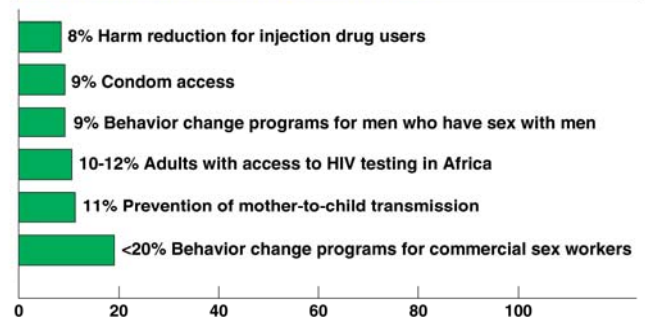
For Every Person Put on Antiretroviral Therapy, 2.5 People are Newly Infected with HIV

HIV Prevention Strategies

Proven:

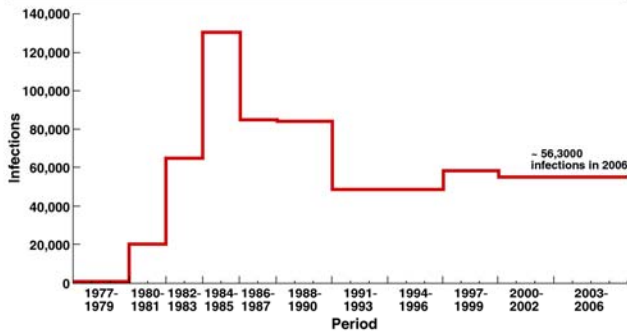
- HIV testing and counseling
- Mass media campaigns
- Education and behavior modification
- Condoms
- Screening of blood supply
- Treatment/prevention of drug/alcohol abuse
- Clean syringes (i.e. "needle exchange" programs)
- ARVs for interruption of transmission from mother to child
- ARVs for post-exposure prophylaxis
- Adult male circumcision

Percentage of Individuals at Risk with Access to HIV Prevention

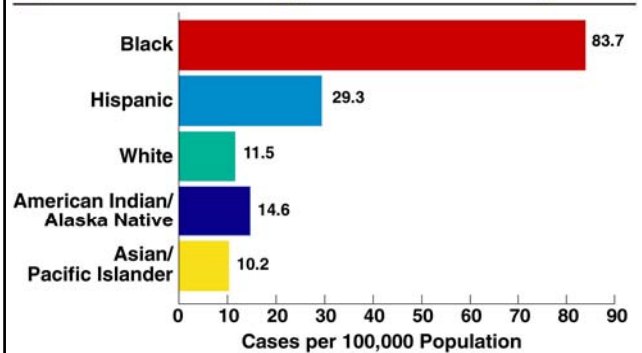


Source: Global HIV Prevention Working Group, 2007; WHO/UNAIDS/UNICEF, 2007

Estimated Number of New HIV Infections Among Adult/Adolescents, USA, 1977-2006



Estimated Rates of New HIV Infections by Race/Ethnicity, United States, 2006



Integrating HIV Testing into Routine Medical Care



Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

Embracing the Concept of Harm Reduction

- Measures to lessen the consequences of high-risk behavior when eliminating the behavior altogether is not realistic, e.g.
 - Sterile needle and syringe access for IDUs
 - Methadone/buprenorphine maintenance treatment
 - Condom provision to commercial sex workers, incarcerated individuals



HIV Prevention Strategies

"Pipeline":

- Preventing/treating co-infections (e.g. TB, malaria, other STDs, parasitic diseases)
- Topical microbicides
- ARVs for uninfected, high-risk individuals (pre-exposure prophylaxis, "PrEP")
- Universal voluntary testing with immediate ARV therapy ("test and treat" strategy)
- Vaccines

Pre-Exposure Prophylaxis (PrEP)

The New York Times

August 4, 2008

Researchers Look to Pill, Taken Daily, to Avert HIV

MEXICO CITY - Can a pill a day help prevent infection from H.I.V., the virus that causes AIDS? No one knows. But researchers in a number of countries are conducting trials and planning others to test the unproven strategy that a daily pill, or a combination of drugs, can prevent H.I.V. . . Up to 15,000 people are expected to be participating in trials by mid-2009.

The Promise of Pre-Exposure Prophylaxis (PrEP)

- Well-established tool for preventing other infectious diseases, e.g. malaria
- ARVs proven to prevent mother-to-child HIV transmission, and as post-exposure prophylaxis
- Generally positive NHP data with tenofovir +/- emtricitabine, drugs with long-half lives, good safety profiles, high genetic barrier to resistance (tenofovir)
- Promise of good acceptability -- PrEP inhibits HIV without requiring change in sexual habits



PrEP: Key Questions/Concerns

- Uncertain efficacy in humans
- Safety / toxicities
- Cost, in a world where <1/3 of people receive needed treatment for established HIV infections
- Adherence
- Emergence of drug resistance
- Increase in risk behavior



"Test and Treat" Concept

THE LANCET

Available online November 27, 2008

Universal Voluntary HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Elimination of HIV Transmission: a Mathematical Model

RM Granich et al.

- Model indicates that universal and annual voluntary HIV testing followed by immediate antiretroviral therapy treatment (irrespective of clinical stage or CD4 count) could reduce new HIV cases by 95% within 10 years
- Concerns: feasibility, protection of individual rights, drug resistance, toxicity, financing

Vaccine

Classical Vaccinology



The response to natural infection provides the proof of concept

Classical Vaccine-Preventable Viral Diseases



Polio



Smallpox



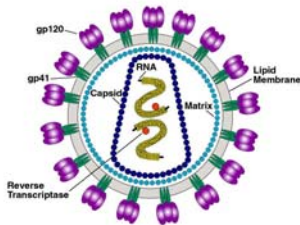
Hepatitis B



Measles

HIV is Different

- The natural immune response to HIV is inadequate
- HIV hides from the immune system
- HIV targets and destroys the immune system
- HIV mutates rapidly



U.S. Department of Health and Human Services
NIH News
National Institutes of Health

FOR IMMEDIATE RELEASE
Friday, September 21, 2007

National Institute of Allergy and Infectious Diseases (NIAID)

<http://www.niaid.nih.gov/>

Immunizations Are Discontinued in Two HIV Vaccine Trials

- Merck product: Ad5 vector expressing *gag*, *pol*, *nef* (clade B)
- Two studies halted
 - STEP (Merck V520-023/HVTN 502)
 - PHAMBILI (HVTN 503)

Classical Vaccinology: Relationship Between Discovery and Development

DISCOVERY

DEVELOPMENT



HIV Vaccinology: “Turning the Knob” Toward Discovery Research

DISCOVERY

DEVELOPMENT



Science

25 July 2008

Follow the Money

HIV Vaccine Research: The Way Forward

AS Fauci, MI Johnston, CW Dieffenbach, DR Burton, SM Hammer, JA Hoxie, M Martin, J Overbaugh, DI Watkins, A Mahmoud, and WC Greene

AAAS

Vaccine

Harm reduction

Education

PrEP

Condoms

Microbicides

Comprehensive HIV Prevention

STI treatment

Circumcision

Testing/
counseling

Drug/alcohol
treatment

ARV therapy



History will judge us as a global community by what we will do in the next 27 years as much as by what we have accomplished in the first 27 years.